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Troponin T, left ventricular mass, and function are excellent predictors of cardiovascular congestion in peritoneal dialysis

AY-M Wang[1,3], CW-K Lam[2], C-M Yu[1], M Wang[1], IH-S Chan[2], S-F Lui[1] and JE Sanderson[1,4]

[1]*Department of Medicine & Therapeutics, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, New Territories, Hong Kong and* [2]*Department of Chemical Pathology, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, New Territories, Hong Kong*

Patients on maintenance peritoneal dialysis (PD) are frequently complicated with volume overload. In this study, we sought to evaluate troponin T testing alone or in combination with echocardiographic measures in predicting cardiovascular congestion in PD patients. This was a prospective study of 222 chronic PD patients with echocardiography and measurement of serum troponin T carried out at baseline. Patients were followed for 3 years or until death. The end point was first episode of cardiovascular congestion. Troponin T emerged as an independent predictor of cardiovascular congestion (hazard ratio, 2.98, 95% confidence intervals (CI), 1.19–7.42) in a multivariable Cox regression model, including also left ventricular mass index (LVMi) and ejection fraction (EF). Patients with troponin T > median (0.06 μg/l) and EF ⩽ 50% and patients with troponin T > median but EF > 50% had a 3.10-fold (95% CI, 1.71–5.63) and 1.88-fold (95% CI, 1.05–3.38) adjusted risk of cardiovascular congestion, respectively, than those with troponin T ⩽ median and EF > 50%. Patients with troponin T > median and LVMi ⩾ median (96.23 g/m$^{2.7}$) had a 2.68-fold (95% CI, 1.39–5.19) adjusted risk of cardiovascular congestion than those with troponin T ⩽ median and LVMi < median. In conclusion, troponin T predicts cardiovascular congestion in chronic PD patients without acute myocardial ischemia and provides incremental prognostic value for cardiovascular congestion when used in combination with LVM and EF. This easily available parameter adds significant value to echocardiography in identifying PD patients at risk of cardiovascular congestion.

Kidney International (2006) **70**, 444–452. doi:10.1038/sj.ki.5001605; published online 28 June 2006

KEYWORDS: end-stage renal disease; heart failure; outcomes; peritoneal dialysis

Correspondence: *AY-M Wang, University Department of Medicine, The University of Hong Kong, Queen Mary Hospital, 102 Pokfulam Road, Pokfulam, Hong Kong. E-mail: aymwang@hkucc.hku.hk*

[3]Current address: Department of Medicine, Queen Mary Hospital, University of Hong Kong, Hong Kong.

[4]Current address: Keele University Medical School, Department of Cardiology, University Hospital of North Staffordshire NHS Trust, City General Hospital, UK.

Received 25 January 2006; revised 22 March 2006; accepted 18 April 2006; published online 28 June 2006

End-stage renal disease patients are at an accelerated risk of developing cardiovascular complications. According to a previous study by Harnett *et al.*,[1] up to a-third of the end-stage renal disease patients on dialysis developed heart failure on initiation of dialysis, of which 56% had further recurrences. Even for patients with no heart failure at baseline, around 25% was complicated with heart failure at a rate of 7% per year. More importantly, the presence of heart failure at initiation of dialysis and its recurrence were both significant predictors of mortality in patients on maintenance dialysis. Thus, the ability to early identify patients at risk of this complication may optimize therapeutic interventions, reduce this complication, and improve the adverse outcomes of dialysis patients.

Echocardiography provides an assessment of left ventricular hypertrophy and dysfunction, and is an important tool in evaluating dialysis patients with heart failure and volume overload. Indeed, the presence of pre-existing systolic dysfunction predisposed dialysis patients to a greater risk of heart failure.[1] Experimental and clinical studies showed that necrosis- or apoptosis-mediated myocyte loss during ventricular remodeling may play a contributory role to the progression of left ventricular dysfunction.[2–6] However, the study of this process requires myocardial biopsy, which is invasive and difficult to perform in humans. Measurement of serum biomarkers that reflect myocyte injury is relatively simple, noninvasive and may allow better characterization of the nature of cardiac disease.

Among these different biomarkers, cardiac troponin T is a highly sensitive and specific marker of myocardial necrosis. Troponin T measurement is useful in diagnosing acute coronary syndrome[7] and is a powerful, independent risk marker in acute coronary syndrome.[8] Troponin T is also increased in patients with heart failure and nonischemic disorders,[9–15] and predicts prognosis in the nonrenal failure population with heart failure, suggesting that troponin T may be a marker of subclinical myocyte injury/necrosis.

Circulating troponin T is frequently elevated in chronic kidney disease and dialysis patients without evidence of acute myocardial ischemia.[16,17] Its elevation has been partly attributed to accumulation of troponin T fragments

secondary to impaired renal clearance.[18] In patients with acute coronary syndrome, troponin T retains its prognostic significance even when renal function is impaired.[19] In addition, elevated troponin T shows important association with left ventricular hypertrophy and dysfunction,[20] and is predictive of mortality and cardiovascular death in end-stage renal disease patients on maintenance dialysis.[21–25] Given that troponin T represents a highly sensitive and specific marker of myocyte injury/necrosis and volume overload is a frequent complication in chronic peritoneal dialysis patients, we hypothesized that troponin T alone or in combination with left ventricular mass and ejection fraction (EF) may serve as important parameters that predict cardiovascular congestion in these patients.

RESULTS

The baseline clinical, demographic, biochemical and dialysis characteristics are shown in Table 1. Eighty-five patients (38.3%) developed cardiovascular congestion during follow-up, of which 49 patients had 1 episode, 19 patients had 2 episodes and 17 patients had 3 or more episodes of cardiovascular congestion. Baseline median (interquartile range) troponin T was 0.1 (0.03, 0.2) μg/l for patients who subsequently developed cardiovascular congestion *versus* 0.03 (0.01, 0.09) μg/l for those who did not ($P<0.001$). Table 2 shows the baseline echocardiographic parameters. Troponin T showed positive correlations with left ventricular mass index (LVMi) by height$^{2.7}$ (Spearman $r=0.44$, $P<0.001$), left ventricular volume in end-diastole index by body surface area ($r=0.46$, $P<0.001$), left ventricular posterior wall thickness in end-diastole ($r=0.33$, $P<0.001$), and interventricular septal wall thickness in end-diastole ($r=0.30$, $P<0.001$) and negative correlations with left ventricular EF ($r=-0.32$, $P<0.001$) and fractional shortening ($r=-0.33$, $P<0.001$).

Predictors of cardiovascular congestion

The univariate Cox regression analysis for cardiovascular congestion is shown in Table 3. Table 4 displays the multivariable Cox regression models for cardiovascular congestion. Troponin T remained an independent predictor of cardiovascular congestion when adjusting for LVMi and EF in addition to other covariates in the base model (Model 3). Kaplan–Meier estimates of cardiovascular congestion-event free probability for all patients according to quartiles of troponin T are shown in Figure 1.

Figure 2a shows the Kaplan–Meier estimates of cardiovascular congestion-event free probability for patients stratifying into four groups on the basis of troponin T $\leqslant$median (0.06 μg/l) and $>$median and LVMi $<$median (96.23 g/m$^{2.7}$) and $\geqslant$median. The prevalence as well as frequency of recurrence of cardiovascular congestion during the 3-year follow-up were the highest among patients with LVMi $\geqslant$median and troponin T $>$median ($P<0.001$; Figure 2b). The multivariable Cox regression analysis with patients stratified into four groups on the basis of troponin T $>$median or $\leqslant$median and LVMi $\geqslant$ median and $<$median is shown in Table 5.

Figure 3a shows the Kaplan–Meier estimates of cardiovascular congestion-event free probability for patients stratifying into four groups on the basis of troponin T $\leqslant$median and $>$median and EF $\leqslant$ 50% and $>$50%. The prevalence as well as frequency of recurrence of cardiovascular congestion during follow-up were the highest among patients with troponin T $>$median and EF $\leqslant$ 50% ($P<0.001$; Figure 3b). Table 6 shows the multivariable Cox regression analysis with patients stratified into four groups on the basis of troponin T $>$median or $\leqslant$median and EF $>$ 50% and $\leqslant$50%.

DISCUSSION

The principal finding of this study was that cardiac troponin T was an independent predictor of cardiovascular congestion in chronic peritoneal dialysis patients. When considered as separate risk factors, troponin T appeared prognostically more important than LVMi or left ventricular EF in determining the risk of cardiovascular congestion. In addition, troponin T provides incremental prognostic value for cardiovascular congestion when used in combination with LVMi and left ventricular EF.

Prognostic value of troponin T for cardiovascular congestion

Studies in the general population showed that 25–50% of patients with heart failure had increased troponin T[26,27] and that increased troponin T correlated with the severity of heart failure,[10–12] and was associated with left ventricular hypertrophy and systolic dysfunction.[14] Increased troponin T was predictive of a worse prognosis in both acute and chronic heart failure.[9,26–28] In patients with nonischemic dilated cardiomyopathy, persistently elevated troponin T was associated with further deterioration of heart failure and a worse outcome,[29,30] suggesting that troponin T is a marker of subclinical myocardial injury. In end-stage renal disease, the association between troponin T with left ventricular mass and function[20,31] is further confirmed in this study of peritoneal dialysis patients. Troponin T has also been shown to be associated with mortality and cardiovascular events[23,31] and with coronary atherosclerosis and cardiomyopathy.[23] The current finding that troponin T retained important prognostic value for cardiovascular congestion independent of left ventricular hypertrophy and EF and that troponin T elevation was prognostically more important than left ventricular hypertrophy and systolic dysfunction in predicting cardiovascular congestion when considered as separate risk factors suggests troponin T elevation in chronic peritoneal dialysis patients may signify something more than cardiac hypertrophy and dysfunction or coronary atherosclerosis. As none of the study patients had acute myocardial infarction at the time of study or within recent 1 month before study entry, it is unlikely that troponin T elevation reflects an acute event. We speculate that troponin T elevation may reflect a more gradual process such as subclinical myocardial necrosis or fibrosis and represent a more global marker of diseased myocardium and left ventricular dysfunction, thus explaining

Table 1 | Baseline clinical, demographic, biochemical, and dialysis characteristics

	All patients (*n*=222)	With cardiovascular congestion (*n*=85)	No cardiovascular congestion (*n*=137)	*P*-value
Clinical and demographic data				
Male gender	111 (50%)	44 (51.8%)	67 (48.9%)	0.68
Age (years)	56±12	56.7±11.1	55.2±11.7	0.33
Body mass index (kg/m^2)	23.1±3.4	23.3±3.5	22.9±3.3	0.45
Positive history of smoking	82 (36.9%)	37 (43.5%)	45 (32.8%)	0.11
Diabetes mellitus	67 (30.2%)	35 (41.2%)	32 (23.4%)	0.005
Known clinical atherosclerotic vascular disease	52 (23.4%)	28 (32.9%)	24 (17.5%)	0.008
Renal diagnosis				
Chronic glomerulonephritis	70 (31.5%)	23 (27.1%)	47 (34.3%)	0.08
Diabetic nephropathy	55 (24.8%)	29 (34.1%)	26 (19.0%)	—
Hypertensive nephrosclerosis	29 (13.1%)	11 (12.9%)	18 (13.1%)	—
Others	68 (30.6%)	22 (25.9%)	49 (33.6%)	—
Duration of dialysis, months	26.5 (15, 51)	25 (13, 49)	30 (16, 56)	0.10
Systolic blood pressure (mm Hg)	147±17	152±17	143±16	<0.001
Diastolic blood pressure (mm Hg)	82±10	83±11	82±9	0.55
Medications use				
Erythropoietin	90 (40.5%)	38 (44.7%)	52 (38%)	0.32
Angiotensin converting enzyme inhibitor	55 (24.8%)	23 (27.1%)	32 (23.4%)	0.54
Beta-blocker	116 (52.3%)	46 (54.1%)	70 (51.1%)	0.66
Calcium channel blocker	135 (60.8%)	50 (58.8%)	85 (62%)	0.63
HMG-CoA reductase inhibitors	31 (14%)	14 (16.5%)	17 (12.4%)	0.40
Total number of anti-hypertensives	1.53±0.96	1.67±0.98	1.45±0.94	0.09
Biochemical data				
Hemoglobin (g/dl)	9.14±1.68	8.62±1.60	9.46±1.66	<0.001
Serum urea (mmol/l)	24±14	26±22	23±6	0.17
Serum creatinine (μmol/l)	1027±274	1028±246	1026±291	0.96
Serum albumin (g/l)	28.5±5.1	27.6±5.4	29.1±4.8	0.03
Calcium × phosphorus product (mmol^2/l^2)	4.30±1.33	4.32±1.30	4.29±1.35	0.88
Parathyroid hormone (pmol/l)	42 (19, 75)	37 (19, 67)	44 (18, 82)	0.60
C-reactive protein (mg/l)	2.78 (0.93, 9.03)	3.20 (1.29, 7.07)	2.25 (0.82, 10.01)	0.36
Troponin T (μg/l)	0.06 (0.01, 0.15)	0.1 (0.03, 0.2)	0.03 (0.01, 0.09)	<0.001
Dialysis indices data				
Total urea clearance	1.81±0.43	1.78±0.44	1.83±0.43	0.48
Peritoneal dialysis urea clearance	1.53±0.35	1.51±0.34	1.54±0.36	0.45
Total creatinine clearance, l/week per 1.73 m^2	56.4±21.4	54.7±19.2	57.4±22.7	0.37
Residual GFR, ml/min per 1.73 m^2	0.55 (0, 1.86)	0.49 (0, 1.60)	0.63 (0, 2.01)	0.45
Daily urine volume(l)	0.39±0.53	0.37±0.50	0.40±0.55	0.68
Net daily peritoneal dialysis ultrafiltration (l)	0.95±0.97	0.88±0.98	0.99±0.96	0.42
Total net daily ultrafiltration (l)	1.32±0.97	1.24±0.98	1.37±0.96	0.32
High transporter status by PET	35 (15.9%)	18 (21.4%)	17 (12.5%)	0.08

GFR, glomerular filtration rate; PET, peritoneal equilibration test.
Values are mean±s.d. or median (interquartile range).

its strong and independent association with cardiovascular congestion. Our data provide important evidence that troponin T appears to be a more precise and accurate measure than echocardiographic parameters such as LVMi and EF in predicting cardiovascular congestion in peritoneal dialysis.

Indeed, being a highly sensitive and specific marker of myocardial necrosis, troponin T has been shown to confirm acute myocardial ischemia in the general population[32] and predicts an increased risk of death or adverse cardiac events following an episode of acute coronary syndrome.[8] Even though the degree of troponin T elevation may be confounded by renal impairment,[33] its prognostic value for acute myocardial ischemia remains irrespective of the degree of renal impairment.[22] There is emerging evidence that troponin T, which is frequently elevated in asymptomatic dialysis patients,[20,21] is a powerful predictor of mortality and cardiovascular death.[21–25] Recent meta-analysis indicated that an elevated troponin T > 0.1 μg/l identifies a subgroup of end-stage renal disease patients with poor survival and high risk of cardiac death despite being asymptomatic.[34] The exact mechanism of this association has remained unclear although study has indicated that patients with detectable circulating troponin T showed histologic changes, including patchy fibrosis and degenerative myocyte changes characteristics of heart failure.[35] This gave additional evidence that an elevated troponin T in chronic peritoneal dialysis patients without acute myocardial ischemia may be indicative of subclinical myocardial necrosis or injury and warrants further evaluation.

Table 2 | Baseline echocardiographic parameters

	All patients (*n*=222)	With cardiovascular congestion (*n*=85)	No cardiovascular congestion (*n*=137)	*P*-value
M-mode and 2-D				
LV mass index by height$^{2.7}$ (g/m$^{2.7}$)	104±40	117±44	96±36	<0.001
LV volume in end-diastole index by body surface area (ml/m^2)	65.9±20.3	73.6±22.7	61.1±17.1	<0.001
LVPWd (cm)	1.3±0.3	1.4±0.3	1.3±0.3	0.16
IVSd (cm)	1.5±0.4	1.5±0.4	1.5±0.4	0.15
LV ejection fraction (%)	52.5±8.3	50.3±9.9	53.9±6.8	0.001
LV fractional shortening (%)	33.3±8.6	31.7±9.5	34.2±7.8	0.04
Patients with LV EF≤50%	73 (32.9%)	38 (44.7%)	35 (25.5%)	0.003
Left atrial diameter end-systole (cm)	4.1±0.7	4.4±0.7	4.0±0.7	<0.001
Mitral inflow velocities				
E (cm/s)	79±27	81±26	77±27	0.22
A (cm/s)	92±25	93±25	91±24	0.51
DT[a] (ms)	250±10	230±9	260±11	0.12
DT≤140 ms	20 (9.3%)	9 (11%)	11 (8.3%)	0.51
DT>140 ms	195 (90.7%)	73 (89%)	122 (91.7%)	
E/A[b]	0.9±0.5	1.0±0.6	0.9±0.4	0.26

LV, left ventricular; LVPWd, left ventricular posterior wall thickness in end-diastole; IVSd, interventricular septal wall thickness in end-diastole; EF, ejection fraction; E, early diastolic transmitral flow velocity; A, late diastolic transmitral flow velocity; DT, deceleration time; E/A, ratio of early to late transmitral flow velocity.
Values are mean±s.d.
[a]Deceleration time could be assessed in 215 patients (97%).
[b]E/A ratio could be calculated in 212 patients (95%).

Table 3 | Univariate Cox regression analysis for cardiovascular congestion

Variables	Hazard ratio (95% CI)	*P*-value
Age	1.01 (0.99–1.03)	0.21
Male gender	1.17 (0.76–1.79)	0.48
Positive smoking history	1.63 (1.06–2.51)	0.026
Dialysis duration	0.995 (0.987–1.003)	0.19
Body mass index	1.04 (0.97–1.11)	0.25
Clinical atherosclerotic vascular disease	2.37 (1.50–3.74)	<0.001
Diabetes	2.14 (1.38–3.30)	0.001
Serum albumin	0.93 (0.89–0.97)	0.002
C-reactive protein	1.00 (0.99–1.02)	0.94
Hemoglobin	0.74 (0.64–0.86)	<0.001
Parathyroid hormone	1.00 (1.00–1.01)	0.95
Calcium *phosphorus product	1.04 (0.90–1.22)	0.59
Systolic blood pressure	1.03 (1.02–1.04)	<0.001
Diastolic blood pressure	1.01 (0.99–1.02)	0.94
High peritoneal transport	1.62 (0.96–2.72)	0.07
Residual glomerular filtration rate	0.89 (0.77–1.02)	0.09
Peritoneal dialysis urea clearance	0.81 (0.45–1.45)	0.47
Left ventricular mass index	1.012 (1.007–1.017)	<0.001
Left ventricular ejection fraction	0.95 (0.93–0.97)	<0.001
Troponin T	6.02 (3.10–11.68)	<0.001

CI, confidence interval.

The causes of subclinical myocardial injury are not entirely clear although a number of factors including recurrent episodes of ischemia/infarction in patients with coronary artery disease, ventricular remodeling, abnormalities of the coronary microcirculation,[10,36] and increased wall strain[37] have all been implicated to play a role in mediating the degradation of cardiac myocytes. Myocyte death/necrosis has been hypothesized to be important pathomechanisms for heart failure and contributes to progressive myocardial dysfunction and ventricular remodeling in the general population.[2–6] However, it is currently not known whether similar pathologic process occurs in patients on dialysis. The evaluation of myocyte apoptosis/necrosis requires myocardial biopsy, which is invasive and not without risk. In contrast, troponin T measurement is routinely available in most hospital laboratories at a relatively low cost, is quick and noninvasive. It has the additional advantage of not being confounded by the presence of inflammation, unlike C-reactive protein.

Added value of troponin T to echocardiography for predicting cardiovascular congestion in peritoneal dialysis

Heart failure and volume overload are frequent complications in chronic dialysis patients.[1] Pulmonary congestion was present in 80% of chronic peritoneal dialysis patients with volume overload.[38] Previous study by Zoccali *et al.* has reported the importance of left ventricular hypertrophy and systolic function as predictors of cardiovascular events in asymptomatic dialysis patients independent of other traditional and novel risk factors such as C-reactive protein and asymmetric dimethylarginine. Of note, patients with both left ventricular hypertrophy and systolic dysfunction showed the greatest risk of cardiovascular events.[39] As shown in our study, echocardiography provides an important evaluation of myocardial status and function in patients with cardiovascular congestion. The presence of more severe left ventricular hypertrophy and systolic dysfunction on echocardiography indeed predicts a higher subsequent risk of cardiovascular congestion. Of greater importance is the novel finding that troponin T provides additional prognostic value when used in combination with left ventricular hypertrophy and EF for predicting cardiovascular congestion in chronic

Table 4 | Multivariable Cox regression analysis of factors predicting cardiovascular congestion

	Base model[a]		Model 1		Model 2		Model 3	
	P	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)
Hemoglobin (1 g/dl ↑)	0.016	0.84 (0.72, 0.97)	0.091	0.88 (0.76, 1.02)	0.064	0.87 (0.76, 1.01)	0.081	0.88 (0.76, 1.02)
Serum albumin (1 g/l ↑)	0.010	0.94 (0.89, 0.99)	0.015	0.94 (0.90, 0.99)	0.014	0.94 (0.89, 0.99)	0.062	0.95 (0.90, 1.00)
Diabetes mellitus	0.035	1.64 (1.03, 2.60)	0.036	1.64 (1.03, 2.61)	0.115	1.46 (0.91, 2.35)	0.167	1.40 (0.87, 2.26)
Systolic blood pressure (1 mm Hg ↑)	<0.001	1.03 (1.01, 1.04)	<0.001	1.03 (1.01, 1.04)	<0.001	1.03 (1.01, 1.04)	<0.001	1.03 (1.02, 1.04)
Atherosclerotic vascular disease	0.003	2.08 (1.29, 3.36)	0.007	1.95 (1.20, 3.16)	0.026	1.75 (1.07, 2.87)	0.019	1.80 (1.10, 2.93)
LVMi (1 g/m$^{2.7}$ ↑)	—	—	0.016	1.007 (1.001, 1.012)	0.050	1.006 (1.000, 1.011)	0.143	1.004 (0.999, 1.010)
Ejection fraction (1% ↑)	—	—	—	—	0.014	0.97 (0.94, 0.99)	0.049	0.97 (0.95, 1.00)
Troponin T (1 μg/l ↑)	—	—	—	—	—	—	0.019	2.98 (1.19, 7.42)
Overall χ^2	55.633	—	60.904	—	66.254	—	75.157	—

LVMi, left ventricular mass index; HR, hazard ratio; CI, confidence intervals.
[a]Covariates considered in the initial model were age, diabetes mellitus, positive smoking history, background AVD, dialysis duration, systolic blood pressure, hemoglobin, serum albumin, residual glomerular filtration rate, and high peritoneal transport by peritoneal equilibration test.

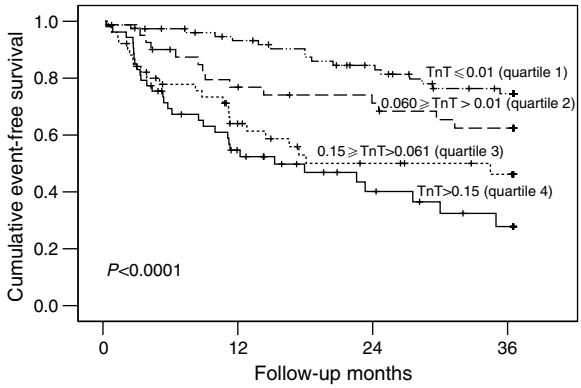

Figure 1 | The Kaplan–Meier estimates of cardiovascular congestion event-free probability in patients stratified by quartiles of troponin T (TnT). Log-rank test showed significant difference in cardiovascular congestion-free probability between Quartile 1 and 3 ($P = 0.0001$), Quartile 1 and 4 ($P < 0.0001$), Quartile 2 and 4 ($P = 0.0025$) but not between Quartile 1 and 2 ($P = 0.12$), Quartile 2 and 3 ($P = 0.10$), and Quartile 3 and 4 ($P = 0.22$).

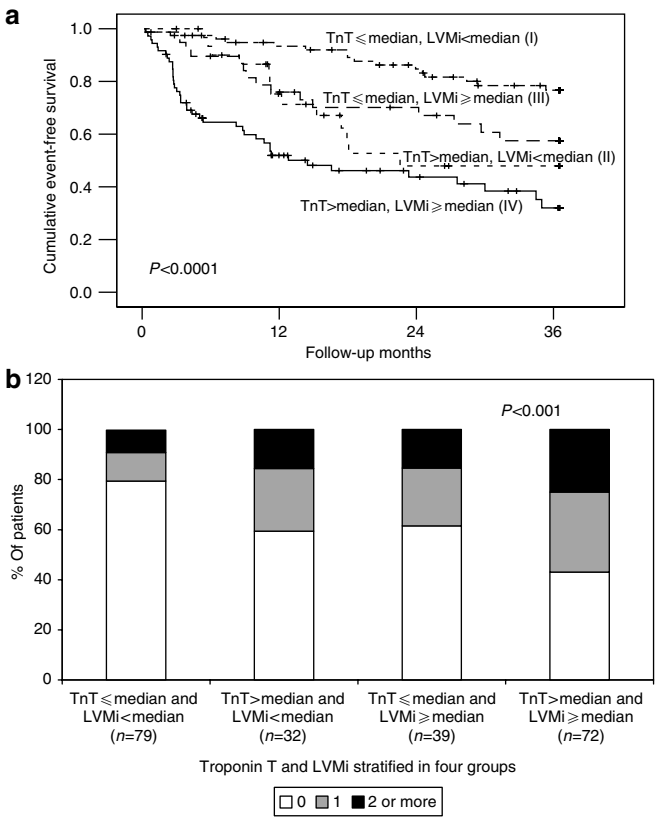

Figure 2 | Episodes of cardiovascular congestion during follow-up. (**a**) The Kaplan–Meier estimates of cardiovascular congestion event-free probability in patients stratified into four groups (groups I–IV) based on the combination of troponin T (TnT) and LVMi. Group I ($n = 79$): TnT ⩽ median (0.06 μg/l), LVMi < median (96.23 g/m$^{2.7}$); group II ($n = 39$): TnT > median, LVMi < median; group III ($n = 32$): TnT ⩽ median, LVMi ⩾ median; group IV ($n = 72$): TnT > median, LVMi ⩾ median. Log-rank test showed significant difference in cardiovascular congestion event-free probability between group I and II ($P = 0.02$), group I and III ($P = 0.001$), group I and IV ($P < 0.0001$), group II and IV ($P = 0.008$), and group III and IV ($P = 0.05$) but not between group II and III ($P = 0.25$). (b) Prevalence and frequency of recurrence of cardiovascular congestion in patients stratified into four groups on the basis of LVMi and troponin T (TnT).

peritoneal dialysis patients. The combination of troponin T with LVMi and EF identifies peritoneal dialysis patients with the greatest risk of cardiovascular congestion. Compared to patients with troponin T ⩽ median and preserved left ventricular systolic function, those with troponin T > median but preserved left ventricular systolic function showed a nearly two-fold increase adjusted risk of cardiovascular congestion while those with troponin T ⩽ median, but systolic dysfunction were at no greater risk of cardiovascular congestion. This suggests troponin T elevation has greater prognostic importance than depressed left ventricular systolic function in determining peritoneal dialysis patients at increased risk of cardiovascular congestion.

In this study, the diagnosis of cardiovascular congestion was made by the attending physician, based on clinical and radiological evidence of pulmonary congestion without implications on the etiologic factor for the episode of cardiovascular congestion. A previous study by our group

Table 5 | Stepwise multivariable Cox regression analysis of predictors of cardiovascular congestion with patients stratified in four groups according to troponin T and LVMi

	P	Hazard ratios	95% CI
Hemoglobin (1 g/dl ↑)	0.061	0.87	0.76, 1.01
Serum albumin (1 g/l ↑)	0.019	0.94	0.89, 0.99
Systolic blood pressure (mm Hg ↑)	<0.001	1.03	1.01, 1.04
Known clinical atherosclerotic vascular disease	0.019	1.80	1.10, 2.95
Left ventricular ejection fraction (% ↑)	0.032	0.968	0.943, 0.997
Troponin T and LVMi stratified in four groups (with troponin T≤median, LVMi <median as reference group)			
Troponin T>median, LVMi <median vs troponin T≤median, LVMi <median	0.097	1.91	0.89, 4.10
Troponin T≤median, LVMi≥median vs troponin T≤median, LVMi < median	0.148	1.72	0.83, 3.58
Troponin T>median, LVMi≥median vs troponin T≤median, LVMi < median	0.003	2.68	1.39, 5.19

CI, confidence intervals; LVMi, left ventricular mass index.

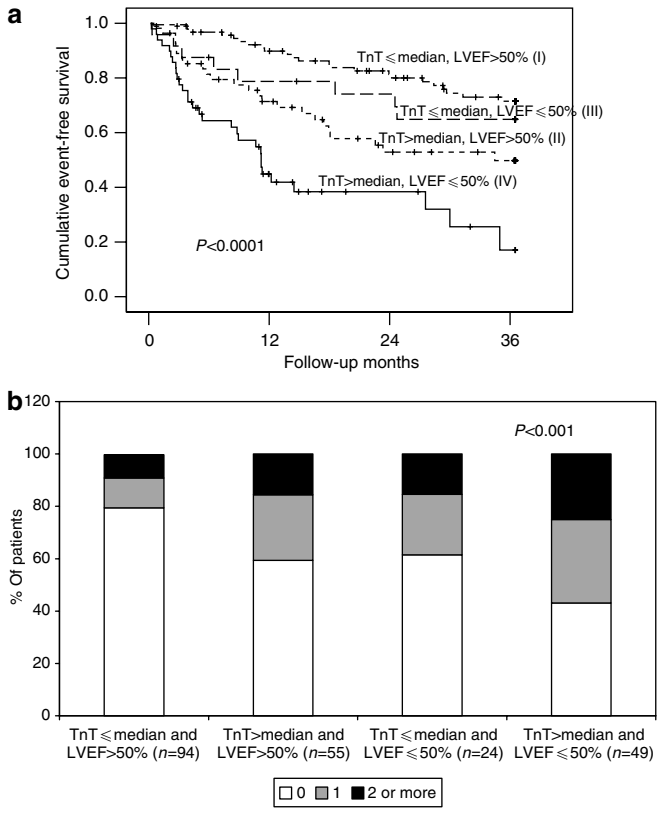

Figure 3 | Episodes of cardiovascular congestion during follow-up. (**a**) The Kaplan–Meier estimates of cardiovascular congestion event-free probability in patients stratified into four groups (groups I–IV) on the basis of troponin T and left ventricular ejection fraction (LVEF). Group I ($n=94$): TnT≤median (0.06 μg/l), LVEF>50%; group II ($n=24$): TnT>median, LVEF>50%; group III ($n=55$): TnT≤median, LVEF≤50%; group IV ($n=49$): TnT>median, LVEF≤50%. Log-rank test showed significant difference in cardiovascular congestion-free probability between groups I and III ($P=0.002$), groups I and IV ($P<0.0001$), groups II and IV ($P=0.005$), and groups III and IV ($P=0.005$) but not between groups I and II ($P=0.38$) and groups II and III ($P=0.25$). (**b**) Prevalence and frequency of recurrence of cardiovascular congestion in patients stratified into four groups on the basis of left ventricular ejection fraction (LVEF) and troponin T.

clearly showed that peritoneal dialysis patients with previous history of cardiovascular congestion, irrespective of the etiology, had greater left ventricular hypertrophy, dilatation and dysfunction.[40] Putting this together with our current finding that troponin T elevation was positively associated with left ventricular mass and negatively associated with left ventricular systolic function and was predictive of subsequent risk of cardiovascular congestion, our results may be interpreted in two ways. Firstly, an episode of cardiovascular congestion even though seemingly reversible with hypertonic exchanges may increase left ventricular hypertrophy, dysfunction, and myocardial damage. Secondly, patients with previous history of cardiovascular congestion may actually remain in a subclinical volume overload state persistently, thus resulting in greater left ventricular hypertrophy and dysfunction. Whichever is the case, troponin T elevation reflects the degree of left ventricular dysfunction more precisely than EF, thus explains its prognostic importance for cardiovascular congestion. Our results are well in keeping with recent study showing that severe coronary artery disease alone could not explain elevated troponin T in dialysis patients.[41] Troponin T elevation reflects myocardial dysfunction and probably subclinical cellular damage as evidenced by left ventricular dilatation, impaired left ventricular systolic function, and raised left ventricular filling pressure.[41]

Study limitations

First, cardiovascular congestion was defined as such to include only episodes that require hospitalization. Patients presenting with milder symptoms of cardiovascular congestion such as ankle edema that do not require hospitalization were considered as event-free. This may result in an underestimation of the true incidence of cardiovascular congestion in our peritoneal dialysis patients. Second, echocardiography was not performed at the time of cardiovascular congestion. Thus, we were not able to determine whether cardiovascular congestion is due to cardiac dysfunction or fluid noncompliance. However, even with echocardiography this distinction is not easy. Third, a single troponin T was measured at study baseline and did not take into account of changes over time. Fourth, the study was performed in end-stage renal disease patients on maintenance peritoneal dialysis. Whether our results can also be generalized to hemodialysis patients and patients

Table 6 | Stepwise multivariable Cox regression analysis of predictors of cardiovascular congestion with patients stratified in four groups according to troponin T and left ventricular ejection fraction

	P-value	Hazard ratios	95% CI
Hemoglobin (1 g/dl ↑)	0.048	0.65	0.75, 1.00
Serum albumin (1 g/l ↑)	0.034	0.95	0.90, 1.00
Systolic blood pressure (1 mm Hg ↑)	<0.001	1.03	1.01, 1.04
Known clinical atherosclerotic vascular disease	0.005	1.99	1.23, 3.21
Troponin T and LVEF stratified in four groups (with troponin T≤median, LVEF>50% as reference group)			
troponin T>median, LVEF>50% vs troponin T≤median, LVEF>50%	0.034	1.88	1.05, 3.38
troponin T≤median, LVEF≤50% vs troponin T≤median, LVEF>50%	0.398	1.42	0.63, 3.19
troponin T>median, LVEF≤50% vs troponin T≤median, LVEF>50%	<0.001	3.10	1.71, 5.63

CI, confidence intervals; LVEF, left ventricular ejection fraction.

with other stages of chronic kidney disease need further evaluation.

Implications

Our study has several important implications. First, given that troponin T remains a powerful predictor of cardiovascular congestion in chronic peritoneal dialysis patients independent of left ventricular mass and systolic function, this strengthens the utility of troponin T testing as a regular cardiovascular risk assessment and monitoring tool in peritoneal dialysis patients without acute myocardial ischemia. Second, the finding that troponin T testing has additional prognostic value to conventional echocardiographic parameters suggests troponin T should be measured in conjunction with echocardiography for cardiovascular risk stratification in order to identify peritoneal dialysis patients at risk of cardiovascular congestion. Third, in view that troponin T elevation in peritoneal dialysis patients may reflect subclinical myocardial injury rather than acute coronary syndrome, the correct troponin T cutoff for diagnosing acute coronary syndrome in peritoneal dialysis patients needs to be re-defined.

Conclusions

Troponin T is a powerful, independent predictor for cardiovascular congestion and adds significant value to echocardiography in identifying peritoneal dialysis patients at risk of cardiovascular congestion.

MATERIALS AND METHODS

Study design and patients

The study protocol was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong. All patients provided informed consent prior to study entry. The study population consisted of 222 consecutive end-stage renal disease patients receiving continuous ambulatory peritoneal dialysis treatment at the outpatient dialysis unit of the Prince of Wales Hospital, Hong Kong and they represented 82% of the total peritoneal dialysis population ($n=270$) at the unit. Patients were considered eligible for study inclusion if they have received peritoneal dialysis treatment for 3 months or more. The remaining 18% of patients were excluded based on the exclusion criteria which included patients with acute coronary syndrome, acute heart failure, underlying malignancy, chronic liver disease, systemic lupus erythematosus, chronic rheumatic heart disease, congenital heart disease, patients who refused to give consent, patients on automated peritoneal dialysis, or patients with incomplete data. All patients were dialyzed using conventional lactate buffered glucose-based peritoneal dialysis solutions.

This study is based on a prospective cohort who was followed up longitudinally for 3 years from the day of study entry. At study entry, baseline echocardiography was performed together with measurement of residual renal function and indices of dialysis adequacy. At the same time, blood samples were collected for measurement of troponin T and other biochemical parameters. Demographic and clinical data of study patients were also recorded at study entry. Known clinical atherosclerotic vascular disease was defined as the presence of ischemic heart disease (indicated by history of angina, previous myocardial infarction with or without history of coronary artery bypass surgery or stenting), cerebrovascular disease (indicated by history of cerebrovascular event or transient ischemic attack), and peripheral vascular disease (indicated by the presence of intermittent claudication or resting leg pain, together with clinical signs of peripheral vascular disease with or without history of amputation or revascularization). The systolic and diastolic blood pressure measured on every follow-up visit at 8-week intervals for the 12 months preceding study entry were averaged to give the final systolic and diastolic blood pressure in each patient.

Echocardiography

Two-dimensional echocardiography was performed using a GE-VingMed System 5 echocardiographic machine (GE-VingMed Sound AB, Horten, Norway) with a 3.3 mHz multiphase array probe in subjects lying in the left decubitus position by a single experienced cardiologist blinded to all clinical details of patients. All echocardiographic data were recorded according to the guidelines of the American Society of Echocardiography.[42] Mitral inflow velocities and diastolic filling were assessed by Doppler echocardiography as previously described.[43] Left ventricular mass was indexed by height rather than body surface area in order to minimize potential distortion by extracellular volume expansion. Left ventricular mass indexed by height has been shown to provide more powerful prediction for mortality and cardiovascular events.[44] Left ventricular hypertrophy was defined as LVMi >47 g/m$^{2.7}$ in women and >50 g/m$^{2.7}$ in men. The EF was obtained using a modified biplane Simpson's method from apical two and four chamber views.[45]

Biochemical measurements

Ethylene diaminetetraacetic acid and heparin blood samples were collected at baseline for measurement of troponin T, C-reactive

protein, albumin, and hemoglobin. Troponin T in ethylene diaminetetraacetic acid plasma was measured by electrochemiluminescence immunoassay (Roche Modular analyzer, Roche Diagnostic GmbH, Mannheim, Germany) with a detection limit of 0.01 μg/l and an inter-assay coefficient of variation of 4.8% at 0.18 μg/l. C-reactive protein and albumin in heparin plasma were measured, respectively, using the Tina-quant C-reactive protein latex high sensitive assay (detection limit of 0.01 mg/l and coefficient of variation of 1.6% at 2.0 mg/l) and the bromocresol purple method (coefficient of variation of 2.8% at 45 g/l) on the Roche analyzer.

Indices of dialysis adequacy

Residual glomerular filtration rate was measured as the average of 24-h urine urea and creatinine clearance.[46] Adequacy of dialysis was estimated by measuring total weekly urea clearance and creatinine clearance using standard methods.[47] Creatinine concentration in dialysate was corrected for interference by glucose according to the reference formula determined in our laboratory.[48] Contribution of peritoneal dialysis and renal component to the total urea clearance was estimated separately. Total body water was derived using the Watson formula.[49] A standard peritoneal equilibration test was performed to determine the peritoneal transport characteristics.

In patients who developed acute coronary syndrome, acute cardiovascular congestion, peritonitis, exit site infections or any other infective complications, all the above assessments were deferred for at least 1 month after complete resolution of the complication.

Outcome measure

All patients were prospectively followed up for 3 years from the day of the baseline assessments or until death or permanent transfer to alternative mode of renal replacement therapy. No patient was lost to follow-up. The outcome measure was the first episode of cardiovascular congestion. The outcome was defined '*a priori*' and the cohort was purposely assembled to examine this complication. Cardiovascular congestion was defined as such to include only episodes that were clearly documented to require hospitalization. This was assessed by using the computerized Clinical Management System of the Hong Kong Hospital Authority and the Renal Registry Database, developed and maintained by the Hong Kong Central Renal Committee and they keep detailed record of all hospitalization episodes. Essentially, the diagnosis was established by the attending physician based on the presence of the following three clinical criteria without preceding knowledge of the troponin T result: first, presence of symptoms and signs of heart failure including dyspnoea, raised jugular venous pressure and basal crepitations; second, radiographic evidence of pulmonary venous congestion or interstitial edema;[1] third, resolution of symptoms, signs and radiographic changes with hypertonic peritoneal dialysis exchanges. In patients who presented to the outpatient clinic with milder symptoms of cardiovascular congestion including ankle edema or facial puffiness and not requiring hospitalization, the episode would not be counted as cardiovascular congestion.

Statistical analysis

Continuous data are represented as mean $\pm$ s.d. or median (interquartile range) depending on the distribution. Comparisons between patients with and without cardiovascular congestion were performed by the *t*-test, Mann–Whitney *U*-test or χ^2 test, as appropriate. Correlations were tested using Spearman rank correlation analysis. Patients were stratified into quartiles according to their baseline troponin T concentrations. Survival analysis was based on the time to develop the first event of cardiovascular congestion. Survival curves of the four quartiles were generated by the Kaplan–Meier estimates and differences in survival among the four quartiles were compared by the Mantel log-rank test. Patients were censored at the time of transfer to alternative renal replacement therapy or at their death.

To evaluate the effect of baseline troponin T in predicting cardiovascular congestion, relative risks and 95% confidence intervals (CI) were calculated as hazard ratios derived from the Cox proportional-hazards regression model. Factors with $P<0.25$ in the univariate analysis (excluding terms for LVMi, left ventricular EF, and troponin T) were first considered in the multivariable Cox regression analysis. A backward elimination procedure (with $P<0.05$) was applied to choose the base model. Subsequent multivariable Cox regression analyses were performed by sequentially adding LVMi, EF, and troponin T as continuous variables to the base model. In order to further evaluate how troponin T influenced the prognostic value of LVMi for cardiovascular congestion, patients were stratified into four groups on the basis of troponin T $>$ median or $\leqslant$ median and LVMi $\geqslant$ median and $<$ median. Survival curves were generated by means of the Kaplan–Meier estimates and differences in survival among the four groups were compared by the Mantel log-rank test. Multivariable Cox regression models were additionally performed, considering the same covariates in the basic model and including terms for LVMi, EF, and troponin T. However, in these models, troponin T and LVMi were entered as a combined nominal variable, stratified into four groups as described above (with troponin T $\leqslant$ median and LVMi $<$ median as the reference group). A backward elimination procedure (with $P<0.05$) was applied to choose the final model. Similar analyses were carried out with patients stratified into four groups on the basis of troponin T $>$ median or $\leqslant$ median and EF $>50\%$ and $\leqslant 50\%$ (with troponin T $\leqslant$ median and EF $>50\%$ as the reference group). All *P*-values were two-tailed. A *P*-value of less than 0.05 was considered to be statistically significant. Statistical analysis was performed using SPSS version 14.0 (SPSS, Inc., Chicago, Illinois, USA).

ACKNOWLEDGMENTS

The study was supported by the Hong Kong Health Service Research Fund 6901023.

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